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# The effect of thyroid autoimmunity on early pregnancy serum β-hCG levels in spontaneous pregnancy

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## ABSTRACT

**Aims**: To examine the association between thyroid autoimmunity (TAI) and early pregnancy serum beta human chorionic gonadotropin (β-hCG) levels in spontaneous pregnancy.

**Methods**: In this retrospective case-control study, women between the ages of 20 and 40 were included. The study subjects were 130 women euthyroid and healthy patients with spontaneous pregnancy. Subjects were divided into two groups: those with autoimmune thyroid disease (TAI group; n=60) and those without the disease (control group; n=70).

**Results**: The mean age and body mass index (BMI) of the subjects were 30.22±4.14 years and 24.51±2.04, respectively. The value of anti-thyroid peroxidase antibodies (TPO-Abs) and anti-thyroglobulin antibodies (TG-Abs) in the TAI group is three times twenty times more than the control, respectively. Results found no statistically significant association between TAI and control groups in regard to hemoglobin, alanine transaminase (ALT), aspartate transaminase (AST), thyroid-stimulating hormone (TSH), platelet (PLT), creatinine, free thyroxin (FT4), and blood urea nitrogen (BUN) ($p>0.05$). There was statistically significant difference between groups in terms of the serum β-hCG level ($p<0.05$).

**Conclusion**: In this study, the effects of TAI were significant on early-stage pregnancy serum β-hCG levels; therefore, thyroid levels should be considered, and proper treatment should be started early.

**Keywords**: Thyroid autoimmunity, β-hCG, pregnancy, miscarriage

## INTRODUCTION

To establish and keep the pregnancy, the immune and endocrine systems should work harmoniously to preserve normal function while adjusting to new conditions.[1] Consequently, immune and endocrine disorders or combined forms could negatively affect the reproductive system.[2] Thyroid autoimmunity (TAI) is estimated to have a prevalence of 5% to 15% as the most prevalent autoimmune disorder among women of reproductive age.[3]

This is the first autoimmune disease discovered by a Japanese doctor, Hakaru Hashimoto, in 1912, and the condition was registered in his name.[4] This disease is characterized by anti-thyroglobulin antibodies (TG-Abs) and anti-thyroid peroxidase antibodies (TPO-Abs) with antibody-dependent cell-mediated cytotoxicity against human thyroid cells.[5,6] Increasing values of TG-Abs and TPO-Abs indicate Hashimoto's thyroiditis leading to hypothyroidism. The increasing stimulating TSHR-Abs cause hyperthyroidism as the hallmark of Graves' disease. Both conditions can be regarded as the opposite ends of TAI's endless diversity.[7] There is an increasing risk of developing subclinical and overt hypothyroidism among TAI women, which has been extensively known for its negative effect on fertility, spontaneous and in vitro fertilization (IVF) reached outcomes of pregnancy.[8-10]

However, increasing evidence shows that TAI may affect reproductive health independently of thyroid hormone levels.[11] According to the hypothesis, the thyroid autoantibodies may disturb the normal process of fertilization, implantation, folliculogenesis, and even embryo development after implantation through various immunological mechanisms, leading to adverse outcomes of a pregnancy conceived either via assisted reproductive technologies or spontaneously.[12,13]

One of the biomarkers of fetal viability is serial serum quantitative assessment of beta unit human chorionic

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gonadotropin (β-hCG). To improve determination of embryonic viability, the combined ultrasonography and serial β-hCG measurements are used to ensure the appropriate performance of interventions, particularly in case of ectopic pregnancy.[14] About 20% of the cases causing miscarriage are associated with increasing serum β-hCG levels.[15]

The impact of Hashimoto's thyroiditis on β-hCG in spontaneous pregnancy is still not clear. This study aims to determine whether TAI affects the first β-hCG value in spontaneous pregnancies. Studies in the literature show that β-hCG values are affected by TAI in IVF pregnancies. 1,16 However, there is not enough research on the possible effects of TAI in spontaneous pregnancy.

## METHODS

The Ethics Committee of Medipol University approved this retrospective case-control study. (Date: 26.10.2022, Decision No: 903). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

One hundred thirty women participated in this study between January 2018 and March 2022. Women between the ages of 20 and 40 were included in this study and 70 women have included control group, and 60 women with thyroid autoantibody positivity were included in the case group.

The exclusion criteria were as follows: 1) known chronic disease, 2) age>40, 3) body mass index (BMI)>30, 4) multiple pregnancies, 5) antibody positivity with thyroid stimulating hormone (TSH)> 2.5, 6) those who use drugs to lower TSH and 7) pregnancy with IVF.

The inclusion criteria were as follows: 1) 20-40 years old, 2)with a body mass index between 18 and 30, 3) women with spontaneous pregnancy, 4) TSH<2.5, 5) positive thyroid antibodies and 6) single pregnancies.

TPO-Abs,TG-Abs, free thyroxin(FT4), TSH were studied with ECLIA (electrochemiluminescence immunoassay) (Roche Diagnostics GmbH, D-68298 Mannheim). TSH was measured with an analytical sensitivity of 0.005 µIU/mL. The TG-Abs measurement range is 10–4000 IU/mL, and the TPO-Abs measurement range is 5–600 IU/mL. TG-Abs < 115 IU/mL, TPO-Abs < 35 IU/mL were accepted as negative. ELISA (BioVendor, Heidelberg, Germany) was used to measure serum TSH and T4 concentrations. the DIAPLUS kit (Toronto, Canada) protocol was followed to perform this hormone assay. The reference ranges of FT4 and TSH were 4.4-10.8 µg/dl and 0.39-5.95 µg/dl, respectively. a double - blind procedure was used to diminish the experimental bias.

### Statistical Analysis

The Statistical Package for Social Sciences software (SPSS 22.0, Chicago, IL) was employed for statistical analyses. The Kolmogorov-Smirnov test was conducted to study the normality, and the parametric (Independent t-test) and the nonparametric (Mann-Whitney U test) tests were performed to study the difference between the two groups. Mean, median, minimum, maximum, and standard deviations (SD) were measured as descriptive statistics for each variable, including age, BMI, hemoglobin, platelet (PLT), alanine transaminase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine, β-hCG, TG-Abs, TPO-Abs, FT4, and TSH. A value of $p<0.05$ was accepted as statistically significant. To calculate the sample size with the GPower 3.1 program, two independent means(two groups) was measured based on the Independent test, the power of 85%, effect size of 50%, and 0.05 type 1 error for at least 118 patients.[17]

## RESULTS

This study included one hundred thirty age-matched (30.22±4.14) and BMI-matched (24.51±2.04) women. The majority of study participants smoke (54.6%). Nine (15%) women in the TAI group and 13 (17.1%) in the control group, a total of 22 women who participated in the study, had abortions. **Table 1** displays descriptive statistics of research parameters.

**Table 1. Descriptive statistics of research parameters (n=130).**

| Research parameters | Median (range) mean ± SD |
|---|---|
| **Maternal characteristics** | |
| Age | 31 (21-36) 30.22±4.14 |
| BMI | 25 (18.4-29.6) 24.51±2.04 |
| **Laboratory values** | |
| Hemoglobin | 12 (10.1-13) 11.64±0.66 |
| PLT | 253000 (140000-486000) 257553.85±72208.36 |
| ALT | 14 (8-51) 15.05±6.42 |
| AST | 15 (10-41) 16.52±5.75 |
| BUN | 16 (4.6-29) 17.37±4.88 |
| Creatinine | 0.71 (0.5-0.92) 0.71±0.11 |
| β-hCG | 119 (40-196) 114.66±42.41 |
| TPO-Abs | 27 (10-65) 34.01±19.15 |
| Anti -TG | 4 (1-90) 19±22.2 |
| FT4 | 1 (0.31-1.62) 1.04±0.28 |
| TSH | 1.63 (0.63-2.46) 1.56±0.53 |

SD, Standard Deviation; BMI, body mass index; PLT, Platelet; ALT, alanine transaminase; AST, Aspartate transaminase; BUN, blood urea nitrogen; β-hCG, Beta human chorionic gonadotropin; TPO-Abs, Anti-thyroid peroxidase; TG-Abs, anti-thyroglobulin; FT4, Free thyroxin; TSH, thyroid-stimulating hormone.

**Table 2** shows comparison of TAI group and control groups on the research parameters.

As stated in **Table 2**, a Mann-Whitney test did not find a statistically significant association between TAI and control groups in regard to Hemoglobin, ALT, AST, TSH, and BUN ($p>0.05$).

As stated in **Table 2**, an Independent test did not find a statistically significant association between TAI and control groups in regard to PLT, Creatinine and FT4 ($p>0.05$). The value of TPO-Abs in the TAI group is three times more than the control. The value of TG-Abs in the case group is twenty times more than the control.

The serum β-hCG level is the main parameters of this research. There was statistically significant difference between groups in terms of the serum β-hCG level ($p<0.05$). The serum β-hCG level of control group (125.31±39.6) was significantly higher than the TAI group (102.23±42.51).

**Table 2. Comparison of TAI group and control groups**

| Study parameters | Thyroid autoantibody negative Control (n=70) Median (range) mean ± SD | Thyroid autoantibody positive Case (n=60) Median (range) mean ± SD | p-value |
|---|---|---|---|
| Hemoglobin | 12 (10.1-13) 11.62±0.73 | 12 (10.4-13) 11.65±0.58 | 0.208* |
| PLT | 249500 (153000-486000) 257985.71±67466.9 | 256000 (140000-455000) 257050±77951.62 | 0.942** |
| ALT | 13.5 (8-51) 15.03±7.84 | 14 (10-27) 15.07±4.25 | 0.163* |
| AST | 15 (10-38) 16.6±5.07 | 14 (10-41) 16.43±6.5 | 0.278* |
| BUN | 20 (4.6-29) 17.4±5.2 | 15.7 (8.4-29) 17.33±4.52 | 0.864* |
| Creatinine | 0.72 (0.5-0.92) 0.71±0.11 | 0.71 (0.52-0.9) 0.71±0.11 | 0.976** |
| β-hCG | 133.5 (40-196) 125.31±39.6 | 101.5 (42-189) 102.23±42.51 | 0.002** |
| TPO-Abs | 15 (10-38) 16.96±6 | 54 (45-65) 53.9±3.57 | <0.001* |
| TG-Abs | 2 (1-5) 2.44±1.09 | 34 (9-90) 38.33±19.25 | <0.001* |
| FT4 | 0.99 (0.53-1.54) 1.04±0.28 | 1.02 (0.31-1.62) 1.04±0.29 | 0.939** |
| TSH | 1.37 (0.63-2.46) 1.53±0.53 | 1.76 (0.65-2.41) 1.59±0.53 | 0.466* |

SD, Standard Deviation; n, number of subjects; PLT, Platelet; ALT, alanine transaminase; AST, Aspartate transaminase; BUN, blood urea nitrogen; β-hCG, Beta human chorionic gonadotropin; TPO-Abs, Anti-thyroid peroxidase; TG-Abs, anti-thyroglobulin; FT4, Free thyroxin; TSH, thyroid-stimulating hormone. *Mann-Whitney U test. **Independent t-test

**Figure 1** shows the difference between two groups (Thyroid autoantibody negative and Thyroid autoantibody positive) on β-hCG.

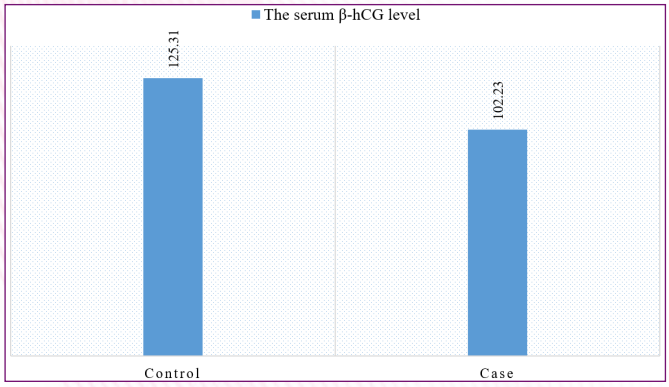


**Figure 1.** Comparison of case and control groups

## DISCUSSION

This study showed that serum β-hCG levels are lower in patients with TAI in the early stage of spontaneous pregnancy. There was no significant statistical difference between the two groups of the TAI and controls in terms of other parameters. There is no study on serum β-hCG levels in patients with TAI in spontaneous pregnancy. This study investigated this case for the first time.

Thyroid hormone dysfunction is associated with a wide-ranging of reproductive system disorders from short luteal phases, premature delivery, miscarriage, failure to sustain a fertilized egg, menstrual irregularities, and infertility.[18] Since the 1950s, researchers have realized the impact of hypothyroidism on blood flow and cycle length in the menstrual cycle.[19] Oligomenorrhea or menorrhagia, infertility, and pregnancy loss indicate hypothyroidism, but these reproductive abnormalities have no well-known causes.[20] There are thyroid hormone receptors in oocytes of primordial, primary, endometrial stromal, and Ishikawa cells, secondary follicles, and human ovarian surface epithelium. TSH-stimulated granulosa cells significantly increased the concentration of cyclic adenosine monophosphate (cAMP) through activation based on the TSH receptor.[21] The thyroid hormone should be available in oocytes for maturation. Thyroid disorders are known as one of the causes of ovulation failure.[10]

TAI and thyroid hormonal dysfunction are associated with an increased risk of adverse pregnancy outcomes.[22] Moleti et al.[23] indicated that TAI poses a risk for preterm delivery and miscarriage. Huget Penner et al.[24] reported that maternal thyroid disease including maternal hypothyroxinemia, hyperthyroidism, hypothyroidism, thyroid autoantibodies, and hyperthyroidism increases the risk of these diseases in the fetus. Toloza et al.[25] reviewed the studies on the relationship between maternal thyroid function and pre-eclampsia. Thyroid disorders were associated with a higher risk of gestational hypertension and pre-eclampsia. Sitoris et al.[26] showed that TAI increased the risk of admission of the baby to the NICU, low birth weight, and preeclampsia. Busnelli et al.[27] reported that TAI increases the risk of miscarriage in women. The adverse effects of TAI on pregnancy outcomes in women have been reported in many studies. However, there is still controversy about the relationship between infertility and TAI.[1,29] Dosiou 28 reviewed recent studies in the field of infertility and thyroid. The thyroid affects women's reproductive system by affecting thyroidal stimulation from β-hCG.

The serum β-hCG level, or pregnancy hormone, is a type of glycoprotein with a lipid framework whose prominent role in pregnancy is to support the corpus luteum.[30] β-hCG is used in predicting, diagnosing, and treating some diseases and as an important prognostic marker showing early pregnancy outcomes.[31] Liu et al.[32] demonstrated higher levels of β-hCG as an essential mediator in the association of higher levels of β-hCG in early pregnancy with a lower risk of gestational diabetes mellitus. Korevaar et al.[33] reported that HCG treatment negatively affects TPO-Abs positivity of pregnancy thyroid response. The damaging effect of thyroid antibodies on the developing embryos or oocytes can cause adverse pregnancy outcomes.[27]

In the current study, lower levels of β-hCG were monitored in patients with TAI compared to the control group. This finding indicates a possible significant relationship between TAI and adverse pregnancy outcomes. Conducting a study with more participants is recommended to investigate this relationship more closely. Following the patient until delivery and examining the fetus's health can produce valuable findings. A decrease in

hCG is seen in ectopic pregnancies and premature labor. Clinicians should have a more detailed follow-up of hCG levels in women with TAI to avoid harmful effects on the fetus and the pregnancy process.

The main limitation of this study is the lack of follow-up on the condition of women in the study until the end of pregnancy. These women's conditions and the child's health after delivery will be investigated in future studies. In this way, the effect of thyroid autoimmunity in spontaneous pregnancy can be seen more accurately and clearly. It is recommended that more studies be conducted to evaluate the effectiveness of the serum β-hCG levels of TAI in spontaneous pregnancy, paying more attention to the genetic and demographic characteristics of women of reproductive age.

## CONCLUSION

This study showed that the level of serum β-hCG in the early stages of spontaneous pregnancy is lower among women with TAI. This result can be used to predict the possibility of early pregnancy loss in pregnant women with TAI. Therefore, thyroid levels should be considered, and proper treatment should be started early.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Medipol University Ethics Committee (Date: 26.10.2022, Decision No: 903).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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